IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 8727
KIM *et al.*	Art Unit: 1627
Appl. No.: 10/646,145	Examiner: SOROUSH, Layla
Filed: August 22, 2003	Atty. Docket: 2298.0140001/TJS/M-N
For: **Composition Comprising the Extract of Actinidia Arguta and Related Species for the Prevention and Treatment of Allergic Disease and Non-Allergic Inflammatory Disease**	

Declaration of Sunyoung Kim Under 37 C.F.R. § 1.132

Mail Stop Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

The undersigned, Sunyoung Kim, Ph.D., residing at 390 Egok-ri Soheul-eup Pocheon-si, GyeongGi-Do, Korea 487-821, declares and states as follows:

1. I am a professor of the Seoul National University. I am also a major inventor listed in the above-captioned patent application. My credentials are provided in the *curriculum vitae* that is attached to this declaration as Exhibit A. I received my Ph.D. degree in Molecular Genetics, from the University of Oxford. As seen from my attached *curriculum vitae*, I have extensively investigated the therapeutic uses of various natural products, and have particular expertise in isolating fruit extracts for the treatment of inflammatory diseases. I have published several papers related to the development of fruit extracts for disease treatment.

2. It is my understanding that the kiwifruit extract discussed in U.S. Patent No. 6,630,163 ("Murad"), which was cited against U.S. Appl. No. 11/522,511, is an extract of *Actinidia deliciosa.*

3. The results presented in Exhibit B, described below, provide a side-by-side comparison of the effects of the extract of *Actinidia arguta*, *i.e.*, the kiwifruit extract recited in the currently pending claims, and the extract of *Actinidia deliciosa, i.e.*, the kiwifruit extract discussed in Murad, on IgE production in U266B1 cells and IL-4 and IL-5 production in ovalbumin (OVA)-sensitized splenocytes from BALB/c female mice. The data presented herewith was obtained by Viromed Co., Ltd.

4. The following is a description of studies comparing the effects of *Actinidia arguta* and *Actinidia deliciosa* extracts. *Actinidia arguta* and *Actinidia deliciosa* fruits were purchased from a farm specializing in the cultivation of *Actinidia arguta* (Hurstberry, Oregon, USA) and a supermarket, respectively. After air-drying, it was determined that the fruits had a moisture content of <10%. The dried fruit (10g) was extracted three times by heat treatment in distilled water (DW) to yield a water-soluble extract. The water-soluble extract was filtered (No. 2 Filter Paper; 110 mm, Whatman), concentrated using a rotary evaporator, and freeze-dried. Freeze-dried extracts were then dissolved in DW at a concentration of 100 mg/mL and stored at –80 °C until they were ready for use.

5. U266B1 cells (human B cell line useful for studying allergic responses *in vitro*) were cultured in 24 well plates (2×10^5 cells/well) in RPMI-1640 medium supplemented with 10 % FBS, 2 mM L-glutamine, 10 mM HEPES, 1 mM sodium pyruvate, 50 μg streptomycin, and 100 U/ml penicillin (all from Life Technologies) at 37 °C under 5% CO_2. Cells were treated with an allergen, lipopolysaccharide ("LPS") (2 μg /ml), and *Actinidia arguta* or *Actinidia deliciosa* extracts (500 μg/ml). After 7 days of

culture, the cell supernatants were collected to measure the level of IgE in the supernatants by ELISA (total human IgE; AlerChek). The results were expressed as a percentage of inhibitory activity on LPS-mediated IgE production.

6. As shown in Exhibit B, the extract of *Actinidia arguta* decreased the LPS-mediated production of IgE by 70%, while the extract from *Actinidia deliciosa* inhibited IgE production by only 37%. The difference between the levels of IgE inhibition by extracts of *Actinidia arguta* and *Actinidia deliciosa* is statistically significant at $p<0.05$. These results demonstrate that the *Actinidia arguta* extract is approximately 2-fold more potent than the *Actinidia deliciosa* extract at inhibiting IgE production. Accordingly, these results clearly demonstrate the superior ability of the *Actinidia arguta* extract to reduce IgE production as compared to the *Actinidia deliciosa* extract discussed in Murad.

7. BALB/c female mice (7 weeks old) were individually immunized and later boosted by intraperitoneal (i.p.) injections of 20 μg of ovalbumin "(OVA") (grade V; Sigma) emulsified in 2.25 mg of aluminum hydroxide (ImjectAlum; Pierce) on day 0 and day 14, respectively. Non-sensitized (naive) mice did not receive any reagent. On day 24, both OVA-sensitized and naive mice were sacrificed (n=5/group), and the spleens of these animals were isolated to study the production of cytokines in splenocytes using the recall response. Briefly, spleens in each group of mice were obtained, pooled and homogenized under sterile conditions. Splenocytes were filtered through a 60 μm pore nylon sieve to remove large aggregates, washed with HEPES-buffered RPMI-1640 medium, and centrifuged at 1500 rpm for 5 min. After centrifugation, the supernatant was discarded, and the splenocytes were resuspended in

culture medium (RPMI-1640 containing 10% heat-inactivated FBS). The resulting splenocyte suspension was seeded into a 24 well culture plate, while adjusting the final concentration of splenocytes to 5×10^6 cells/ml/well. Splenocytes were incubated with 100 μg/ml of OVA in the presence of *Actinidia arguta* or *Actinidia deliciosa* extract (1 mg/ml, respectively), or media as a control for 3 days. Following incubation, the splenocyte culture supernatants were collected to detect the level of IL-4 and IL-5 using respective ELISA kits (Endogen).

8. As shown in Exhibit C, the extract of *Actinidia arguta* significantly decreased the OVA-stimulated production of IL-4 by 70%, while the extract of *Actinidia deliciosa* inhibited IL-4 production by only 29%. The difference between the levels of IL-4 reduction by extracts of *Actinidia arguta* and *Actinidia deliciosa* is statistically significant at $p<0.05$. These results demonstrate that the *Actinidia arguta* extract is about 2.5-fold more potent than the *Actinidia deliciosa* extract at inhibiting IL-4 production. Accordingly, these results clearly demonstrate the superior ability of the *Actinidia arguta* extract to reduce IL-4 (Th2 cytokine) production as compared to the *Actinidia deliciosa* extract.

9. In conclusion, the results presented in Exhibits B and C clearly demonstrate the superior and unexpected abilities of the extract of *Actinidia arguta* to reduce IgE and Th2 cytokine production as compared to the extract of *Actinidia deliciosa*.

10. I further declare that the above statements made of my own knowledge are true and the above statements based on information and belief obtained from the references and documents discussed are believed to be true. Additionally, I declare that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Title 18 United States Code Section 1001, and that willful false statements may jeopardize the validity of this application or any patent issuing thereon.

11. I have read, I am familiar with, and I understand, the provisions of 37 C.F.R.§§ 11.18(b) and (c) relating to the effect of signature and certificate for correspondence filed in the U.S. Patent and Trademark Office.

Date: Aug 18, 2010

Sunyoung Kim, Ph.D.

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Exhibit A

CURRICULUM VITAE

Name : Sunyoung Kim

Position: Professor

Institution : School of Biological Sciences, Seoul National University

Academic Degrees:

1978	Microbiology	B.S.	Seoul National University
1982	Biochemical Engineering	M.S.	MIT
1984	Microbiology and Molecular Genetics	M.A.	Harvard University
1986	Molecular Genetics	D. Phil	University of Oxford

Professional Activities (Selected):

1987-1989	Postdoctoral fellow Whitehead Institute for Biomedical Research, and Department of Biology, MIT (with Dr. David Baltimore)
1990-1992	Assistant Professor of Medicine (Virology) Harvard University
1992- Present	Professor Seoul National University
1998-present	Member of the Editorial Board Journal of Gene Medicine (John Wiley & Sons Ltd.)
2003-2008	Member of the Editorial Board Gene Therapy (Nature Publishing Group)
2006-2008	President Korea Society of Gene Therapy
2005-2009	Chief Executive Officer, Founder ViroMed Co. Ltd. (Korea)

Publications:

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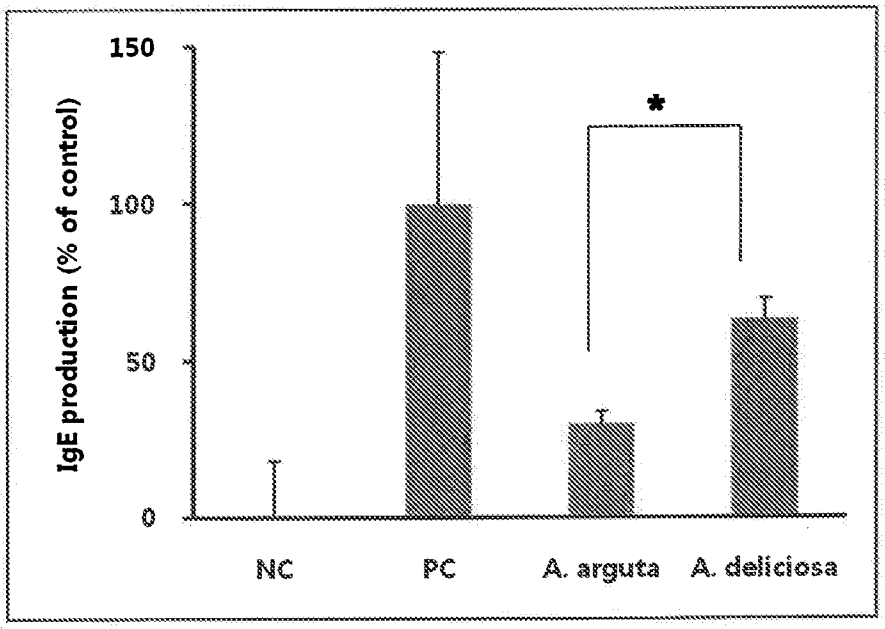
Exhibit B

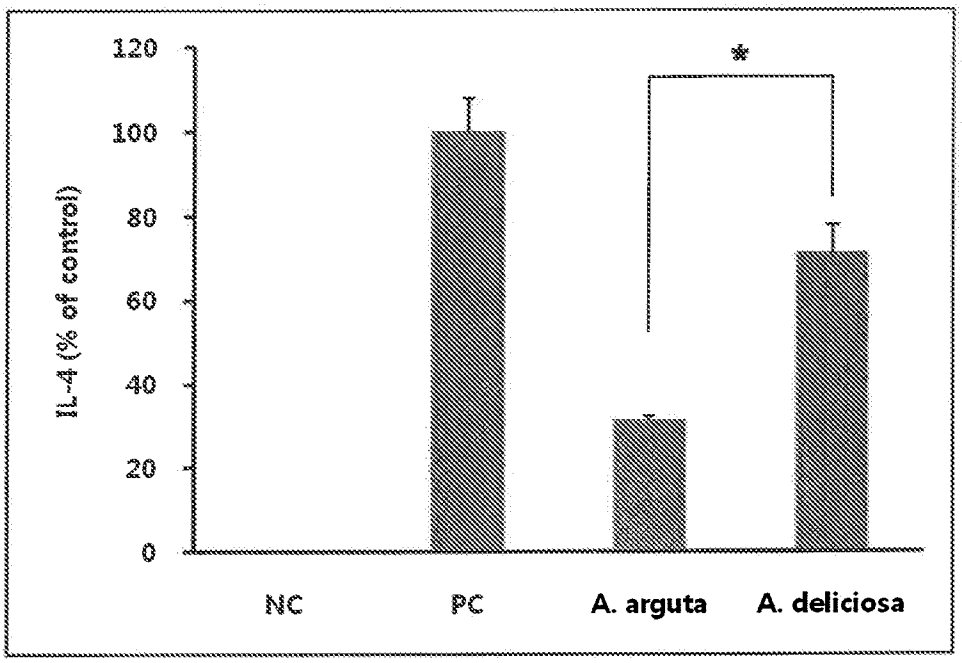


* $p<0.05$

NC = Negative Control

PC = Positive Control

Exhibit C



* $p<0.05$

NC = Negative Control

PC = Positive Control